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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,997	09/18/2003	Carol Carter	FUNC-0017-CO1	6642

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	
MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/666,997	CARTER ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *59-91 and 93-134* is/are pending in the application.

4a) Of the above claim(s) *59-91 and 95-131* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *93,94 and 132-134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

The present application was filed containing a power of attorney to Mr. Steven B. Kelber and Mr. Jerold Schneider. A correspondence address was supplied for Mr. Steven B. Kelber. No address was supplied for Mr. Jerold Schneider.

Mr. Steven B. Kelber was suspended from practice before the Patent and Trademark Office (Office). The Office does not communicate with attorneys or agents who have been suspended or excluded from practice.

As a correspondence address, other than to Mr. Steven B. Kelber, is not of record, this Office action is being mailed to the other practitioner of record at his/her last known address as listed on the register of patent attorneys and agents. To ensure that a copy of this Office action is received in a timely manner to allow for a timely reply, a copy of the Office action is being mailed directly to the address of the inventor first named in the declaration or oath. Any reply by applicant(s) should be by way of the remaining practitioner(s) of record and should include a new correspondence address.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 26 August 2008 has been entered.

DETAILED ACTION

This Office Action is in response to the amendment filed 26 August 2008. Claims 1-58 and 92 have been cancelled. Claims 59-91 and 93-134 are pending. Claims 59-91 and 95-131 are drawn to a nonelected subject matter and hence are withdrawn from further consideration pursuant to 37 CFR 1.142(b). Claims 93, 94 and 132-134 are currently examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 93, 94 and 132-134 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is **maintained**.

Claims 93, 94 and 132-134 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 I[1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988); and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id*. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 93, 94 and 132-134 are directed to a method of inhibiting human immunodeficiency virus (HIV) particle generation in cells comprising administering a peptide comprising a PTAP motif, said compound inhibits binding between tumor susceptibility gene (Tsg101) protein and HIV Gag polypeptide.

The breadth of the claims encompass inhibiting HIV particle formation in any kinds of cells, including *in vivo* and *in vitro*, suspected to be infected by any strain or subtype of HIV by inhibiting the binding of any form of Tsg101 and the Gag protein of any strain or quasi-species of HIV. With the exception of claim 132 limiting the peptide to comprise SEQ ID NO:4, the claimed peptide can be from a PTAP peptide to any protein containing the four amino acids, PTAP. Further, claims 93, 94 and 132 do not claim whether the anti-HIV peptide acts on a target that is conserved among all hosts.

The disclosure does not provide any working embodiments that meet the claimed limitations. While there is one cell culture example (page 37-41) identifying the binding regions of Gag p6 late domain and Tsg101 and mutating by deletion of the binding region in either Tsg101 or Gag protein to observe the effect on particle release by HIV vector-transfected COS cells, there is no *in vitro* or *in vivo* working example that shows the effectiveness of any other PTAP-containing peptides in inhibiting particle formation. Furthermore, the Gag p6 late domain does not represent the entire genus of the PTAP-containing peptides. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable.

The specification provides no guidance regarding practice of the claimed method. The amount of direction is limited to one cell culture assay identifying the binding regions in HIV Gag p6 late domain and Tsg101 (Example 1) and the amount of released mature HIV particles as a result of mutated binding regions in Tsg101 and HIV Gag p6 late domain (Example 2). The disclosed example is not even a test of a peptide inhibitor for the interaction between Tsg101 and Gag. There is no evidence that shows any correlation with *in vivo* efficacy to confirm the Applicant's theory deduced from the cell culture results. There is no teaching about the therapeutic properties such as the binding specificity, selectivity and affinity, oral bioavailability, cellular uptake, toxicity, lethal dose, and side effects for administering a PTAP-containing peptide into a cell inside a body. There is not even a test to determine the efficacy and resistance of the claimed genus of Tsg101 inhibitors. Therefore, the disclosure does not correlate with inhibiting HIV particle formation in cells *in vitro* or *in vivo*.

There is a high level of uncertainty and unpredictability in the art. The development of suitable HIV-1 inhibitors has been an arduous and empirical process, often ending in failure (Hendrix, 2000, first and last paragraph; Gait, 1995). This is due to a number of factors: (1) failure to understand the molecular determinants modulating many viral protein and host cell factor interactions; (2) failure of in vitro tissue culture studies and in vivo animal models to adequately predict clinical efficacy; (3) failure of many compounds to have acceptable pharmacological profiles despite initial favorable in vitro and in vivo activities; and (4) failure of related structural analogs to function in the desired manner, which provides further evidence of the specificity of these

molecular interactions. The challenges of developing efficacious anti-HIV agents are best summarized by Gait and Karn (1995) who state in the Conclusions (p.37): There can be few tasks in biotechnology that are more challenging than designing antiviral drugs. All of the protease inhibitors that have entered into clinical trials are potent inhibitors of HIV-1 replication in cell culture, and exhibit remarkable selectivity for the viral enzyme. Unfortunately, early protease inhibitors tended to suffer from problems of short serum half-life, poor availability and rapid clearance. As these pharmacokinetic problems have been addressed and solved, new difficulties have emerged from the resultant clinical experience, such as sequestration of the drug by serum proteins, drug resistance and uneven distribution throughout the body. Since these types of problems are unpredictable, it remains necessary to take into account the pharmacological parameters in any drug development programme at the earliest possible stage.

The art of HIV particle inhibitors is highly unpredictable because the effect of such a compound appears to change due to pharmacokinetic variation, fluctuating adherence, the emergence of drug resistant mutations and/or other factors. Inadequate drug concentrations can result from a number of factors including non-adherence, pharmacokinetics, and lack of drug potency. In addition, anatomical sanctuary sites may exist where drug concentrations do not achieve adequate levels despite apparent therapeutic serum drug concentrations. HIV replication can occur in such settings, and the selective pressure of antiretroviral therapy leads to the emergence of HIV harboring drug-resistant mutations. Thus, a key element in future drug design strategies is to understand how drug resistance mutations affect the interaction of the drug with its

target, and to then develop compounds with the adaptability to inhibit these variants along with wild-type HIV (Yin, 2006). Therefore, efforts to develop effective treatments must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

In the instant case, a Tsgl01-Gag binding inhibitor as an AIDS drug is not considered routine in the art. The disclosure fails to address any of the aforementioned caveats in the development of an antiviral agent. Without sufficient guidance to the safety, bioavailability, plasma concentration, and antiviral effect, the experimentation left to those skilled in the art is undue or unreasonable under the circumstances.

For the reasons discussed above, it would require undue and unpredictable experimentation for one skilled in the art to use the claimed method.

Response to Arguments

Applicant's arguments filed 26 August 2008 have been fully considered but they are not persuasive. Applicants argue that the claims do not recite efficacy in the treatment of humans. However, the limitation “inhibiting HIV particle generation comprising administering to cells suspected of being infected with HIV” reads on inhibiting HIV particle generation not only in cell cultures but also in human cells in a patient body. The instant specification describes an assay to identify the peptide sequence of the region in HIV Gag protein that is important for HIV particle formation but never discloses any example of a PTAP-containing peptide that is effective in

inhibitions of HIV particle formation. While there is one cell culture example (page 37-41) identifying the binding regions of Gag p6 late domain and Tsg101 and mutating by deletion of the binding region in either Tsg101 or Gag protein to observe the effect on particle release by HIV vector-transfected COS cells, there is no *in vitro* or *in vivo* working example that shows the effectiveness of any other PTAP-containing peptides in inhibiting particle formation. Furthermore, the Gag p6 late domain does not represent the entire genus of the PTAP- containing peptides. The Gag protein is neither conserved between the two HIV serotypes, HIV-1 and HIV-2, nor among the abundant strains or quasi-species of HIV. Therefore, the peptide binding affinity/avidity is questionable.

The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See M.P.E.P. §2164.03 [R-2]. Relationship of Predictability of the Art and the Enablement Requirement. Since the prior art is unpredictable and fails to provide sufficient illumination pertaining to the structural constraints governing viral particle formation, and the disclosure fails to provide sufficient working embodiments to enable the full breadth of the claimed invention, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention.

Applicant argues that the specification explains the mechanism of HIV particle reduction in detail. However, the speculation of preventing the PTAP region of Gag

protein from interacting with Tsg101 is not representative or predictive of the effectiveness of any PTAP-containing peptides. The instant specification discloses at most an assay for identifying all PTAP-containing peptides that are effective at inhibiting the binding between Tsg101 and the HIV Gag protein and thereby blocking the HIV particle generation step in the virus lift cycle. Applicant has not provided any evidentiary basis that validates the theory that a PTAP-containing peptide of any length is an effective inhibitor of Gag-Tsg101 binding and reduces particle formation.

Applicant also argues that the Examiner has affirmatively represented that the claims read on a genus of unspecified compounds, which encompass siRNA, aptamers, ribozymes, antibodies, small molecule inhibitors and Gag homologs. This sentence is lifted out of context in Examiner's office action mailed on 8 August 2007. This sentence was a part of the Examiner's summary of a previous Office Action mailed on 5 June 2006. Since Applicant amended the claims and added the limitation "wherein said compound is a peptide comprising a PTAP motif," the aforementioned sentence is no longer the Examiner's position. The antibody data in the specification of the copending U.S. Application No. 11/040,714 is irrelevant because the disclosed Tsg101 antibodies do not meet the present claim limitation of a peptide comprising a PTAP motif.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648
03 November 2008
/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648